

WHAT IS CLAIMED IS:

1 1. A method of forming an array of polymers on a
2 surface of a substrate, comprising:

3 providing a substrate having a first surface coated
4 with functional groups protected with a photolabile protecting
5 group, and a second surface having a layer disposed thereon,
6 said layer including one or more of an index matching
7 compound, a light absorbing compound and an antireflective
8 compound; and

9 sequentially activating and coupling monomers in
10 different selected regions of said substrate to form a
11 plurality of different polymer sequences in different known
12 locations on said surface of said substrate, wherein said
13 activating step comprises directing an activation radiation at
14 said first surface of said substrate.

1 2. The method according to claim 1, wherein said layer
2 disposed upon said second surface of said substrate comprises
3 an index matching compound.

1 3. The method according to claim 1, wherein said layer
2 disposed upon said second surface of said substrate is an
3 antireflective compound.

1 4. The method according to claim 1, wherein said layer
2 disposed upon said second surface of said substrate comprises
3 an index matching compound and a light absorbing compound.

1 5. The method according to claim 1, wherein said layer
2 disposed upon said second surface of said substrate comprises
3 polyimide.

1 6. The method according to claim 1, wherein said
2 plurality of different polymer sequences comprises a plurality
3 of different oligonucleotide sequences.

1 7. A method of forming a plurality of individual
2 polymer arrays, comprising:

3 providing a plurality of substrate wafers, each of
4 said substrate wafers having a first surface, said first
5 surface having functional groups disposed thereon, said
6 functional groups being protected with a removable protecting
7 group;

8 exposing a plurality of first selected regions on
9 said first surface of each of said substrate wafers to an
10 activator at an activation station to remove said removable
11 protecting groups from said functional groups in said first
12 selected regions;

13 first moving said substrate wafers batch-wise to a
14 coupling station;

15 contacting said plurality of wafers with a monomer
16 containing solution at said coupling station, to couple first
17 selected monomers to said functional groups in said selected
18 regions on said surface of said plurality of substrate wafers;

19 first returning said substrate wafers batch-wise to
20 said activation station;

21 exposing a plurality of second selected regions on
22 said first surface of each of said substrate wafers to an
23 activator at said activation station to remove said removable
24 protecting groups from said functional groups in said second
25 selected regions;

26 second moving said substrate wafers batch-wise to
27 said coupling station;

28 contacting said plurality of wafers with a monomer
29 containing solution in said coupling station, to couple second
30 selected monomers to said functional groups in said selected
31 regions on said surface of said plurality of substrate wafers;

32 repeating said exposing and contacting steps to form
33 a plurality of individual polymer arrays on said first surface
34 of each of said substrate wafers.

1 8. The method according to claim 7, wherein said
2 contacting steps comprise simultaneously contacting said

3 plurality of substrate wafers with said monomer containing
4 solutions.

1 9. The method according to claim 7, wherein said
2 removable protecting group is a photolabile protecting group
3 and said activator is light.

1 10. The method according to claim 7, wherein said
2 exposing step comprises simultaneously contacting at least a
3 first of said plurality of substrate wafers with a first
4 monomer containing solution and contacting a second of said
5 plurality of substrate wafers with a second monomer containing
6 solution.

1 11. The method according to claim 7, wherein said
2 activator comprises an activation radiation and said exposing
3 step comprises directing said activation radiation at said
4 first surface of said plurality of substrate wafers, and
5 wherein a second surface of said plurality of substrate wafers
6 includes a layer of one or more of an index matching compound,
7 a light absorbing compound and an antireflective compound
8 disposed thereon.

1 12. The method according to claim 11, wherein said layer
2 disposed upon said second surface of said substrate comprises
3 an index matching compound.

1 13. The method according to claim 11, wherein said layer
2 disposed upon said second surface of said substrate is an
3 antireflective compound.

1 14. The method according to claim 11, wherein said layer
2 disposed upon said second surface of said substrate comprises
3 an index matching compound and a light absorbing compound.

1 15. The method according to claim 11, wherein said layer
2 disposed upon said second surface of said substrate comprises
3 polyimide.

1 16. The method according to claim 7, wherein said
2 plurality of different polymer sequences comprises a plurality
3 of different oligonucleotide sequences.

1 17. A method of forming an array of polymers on a
2 surface of a substrate, comprising:

3 derivatizing said surface of said substrate by
4 contacting said surface of said substrate with a solution of
5 aminoalkyltrialkoxysilane to provide amine functional groups
6 on said first surface of said substrate;

7 protecting said functional groups with a protecting
8 group;

9 activating first selected regions on said first
10 surface of said substrate by removing said protecting groups
11 from said functional groups in said first selected regions;

12 coupling a first monomer to said functional groups
13 in said first selected regions;

14 activating second selected regions on said first
15 surface of said substrate by removing said protecting groups
16 from said functional groups in said second selected regions;

17 coupling a second monomer to said functional groups
18 in said second selected regions;

19 repeating said activating and coupling steps to form
20 a plurality of different polymer sequences, each of said
21 different polymer sequences being coupled to said surface of
22 said substrate in a different known location.

1 18. The method according to claim 17, wherein said first
2 and second monomers coupled in said coupling steps comprise an
3 active phosphoramidite group.

1 19. The method according to claim 17, wherein said first
2 and second monomers comprise nucleosides.

1 20. The method according to claim 17, wherein said
2 aminoalkyltrialkoxysilane is selected from the group
3 consisting of 3-aminopropyltriethoxysilane and 3-
4 aminopropyltrimethoxysilane.

1 21. The method according to claim 17, wherein in said
2 derivatizing step, said contacting of said surface of said
3 substrate with a solution of aminoalkyltrialkoxysilane is
4 carried out by controlled vapor deposition of said
5 aminoalkyltrialkoxysilane on said surface.

1 22. The method according to claim 17, wherein said
2 plurality of different polymer sequences comprises a plurality
3 of different oligonucleotide sequences.

1 23. A method of forming an array of polymers on a
2 surface of a substrate, comprising:
3 stripping said surface of said substrate with a
4 stripping solution;
5 providing functional groups on said surface of said
6 substrate;
7 protecting said functional groups with a photolabile
8 protecting group;
9 exposing first selected regions on said first
10 surface of said substrate to an activation radiation to remove
11 said photolabile protecting groups from said functional groups
12 in said first selected regions;
13 coupling a first monomer to said functional groups
14 in said first selected regions;
15 exposing second selected regions on said first
16 surface of said substrate wafers to an activation radiation to
17 remove said photolabile protecting groups from said functional
18 groups in said second selected regions;
19 coupling a second monomer to said functional groups
20 in said second selected regions;
21 repeating said exposing and coupling steps to form a
22 plurality of different polymer sequences, each of said
23 different polymer sequences being coupled to said surface of
24 said substrate in a different known location.

1 24. The method according to claim 23, wherein said
2 stripping step comprises contacting said surface of said
3 substrate with a stripping solution of concentrated NaOH/H₂O₂.

1 25. The method according to claim 23, wherein said
2 stripping step further comprises:
3 contacting said surface of said substrate with base;
4 and
5 rinsing said substrate with acid.

1 26. A method of coupling monomers to selected regions on
2 a surface of a substrate, comprising:
3 providing functional groups on said surface of said
4 substrate, said functional groups being protected with a
5 photoprotecting group;
6 exposing said selected regions to an activation
7 radiation to remove said photolabile protecting group in said
8 selected regions, said exposing step comprising directing an
9 activation radiation at said selected regions on said surface
10 of said substrate by shining said activation radiation through
11 a photolithographic mask, said photolithographic mask
12 including transparent regions and opaque regions, said
13 transparent regions being smaller than said selected regions,
14 whereby when said activation radiation is shone through said
15 transparent regions in said mask, said activation radiation is
16 diffracted to expose substantially all of said selected
17 regions; and
18 coupling monomers to said functional groups in said
19 selected regions.

1 27. The method according to claim 26, wherein said
2 transparent regions in said mask are from about 2% to about
3 25% smaller in each dimension than said selected regions.

1 28. The method according to claim 26, wherein said
2 transparent regions in said mask are from about 10% to about
3 20% smaller in each dimension than said selected regions.

1 29. A method of forming polymer sequences on a solid
2 substrate, comprising:
3 providing functional groups on said surface of said
4 substrate;

5 coupling monomers to said functional groups on said
6 surface of said substrate, said monomers having chemical
7 groups reversibly coupled thereto, whereby said chemical
8 groups enhance the lipophilicity of said monomers.

1 30. The method according to claim 29, wherein said
2 monomer comprises a nucleotide protected with a lipophilic
3 protecting group.

1 31. The method according to claim 30, wherein said
2 lipophilic protecting group is coupled to an exocyclic
3 functional group in a nucleobase in said nucleotide.

1 32. The method according to claim 31, wherein said
2 exocyclic functional group is protected with a DMT protecting
3 group.

1 33. The method according to claim 30, wherein said
2 lipophilic protecting group is a photolabile protecting group.

1 34. The method according to claim 30, wherein said
2 monomer comprises a nucleoside Fmoc-phosphoramidite.

1 35. A method of deprotecting an array of polymer
2 sequences synthesized on a solid support, comprising
3 contacting said array with a solution containing a substituted
4 alkylamine.

1 36. The method according to claim 35, wherein said
2 substituted alkylamine is selected from the group consisting
3 of ethanolamine and ethylenediamine.

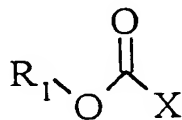
1 37. The method according to claim 35, wherein said
2 solution of substituted alkylamine is a solution of
3 ethylenediamine in ethanol.

38. The method according to claim 35, wherein said solution containing alkylamine is a 1:1 solution of ethylenediamine in ethanol.

39. A method of forming an array of polymer sequences on a surface of a substrate by sequentially deprotecting and coupling monomers in selected regions of said surface of said substrate to produce a plurality of different polymer sequences in different known locations of said surface of said substrate, the method comprising aligning deprotection and coupling steps in adjacent selected regions to minimize a number of differential synthesis steps between said adjacent regions.

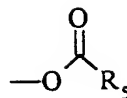
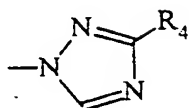
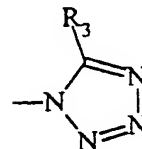
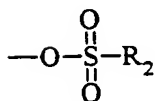
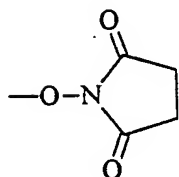
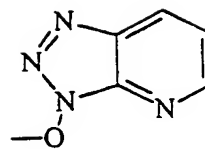
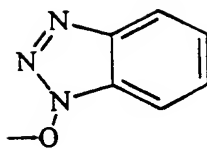
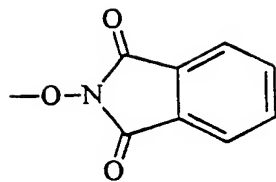
40. A method of forming an array of polymer sequences wherein each polymer sequence has a subsequence of monomers common to a sequence that is complementary to a target sequence, but wherein at least one position within said subsequence is substituted with each member of a basis set of monomers, the method comprising coupling all monomers in a same layer of a first of said polymer sequences in a same synthesis cycle as corresponding monomers in a second of said polymer sequences.

41. A method of photoprotecting a functional group coupled to a solid support, the method comprising exposing said functional group to a photoprotecting group transfer agent having the formula:

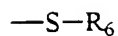
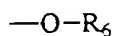


wherein R_1 is a photolabile protecting group and X is a leaving group.

42. The method according to claim 41, wherein X is selected from the group consisting of:



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6 where R_2 is alkyl, substituted alkyl or aryl, R_3 is hydrogen,
 7 alkyl, thioalkyl, aryl; R_4 is an electron withdrawing group;
 8 R_5 is a sterically hindered alkyl or aryl group; and R_6 is
 9 alkyl or aryl group said alkyl or aryl group comprising an
 10 electronegative substituent.

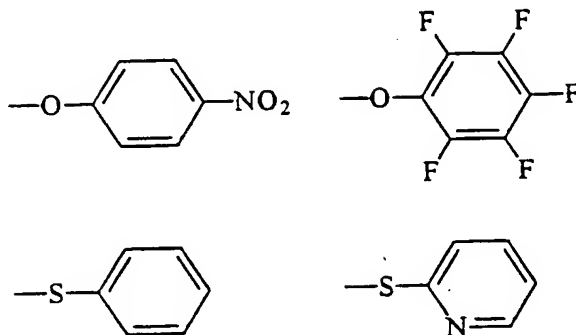
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43. The method according to claim 42, wherein R_4 is
 2 selected from the group consisting of NO_2 , $\text{SO}_2\text{-R}_2$, and CN .

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44. The method according to claim 42, wherein R_5 is
 2 selected from the group consisting of adamantyl and t-butyl.

1 45. The method according to claim 42, wherein said
2 electronegative substituent is selected from the group
3 consisting of:
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1 46. The method according to claim 41, wherein R₁ is
2 selected from the group consisting of NVOC, NPOC, MeNVOC,
3 MeNPOC, PYMOC, NV, NP, MeNV and MeNP.

1 47. The method according to claim 41, wherein said
2 exposing step is carried out in the presence of a non-
3 nucleophilic organic solvent and a base catalyst.

1 48. The method according to claim 47, wherein said non-
2 nucleophilic organic solvent is selected from the group
3 consisting of DMF, NMP, DCM, THF and ACN.

1 49. The method according to claim 47, wherein said base
2 catalyst is selected from the group consisting of pyridine,
3 2,6-lutidine, TEA and DIEA.